REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

I. CLAIM STATUS AND AMENDMENTS

Claims 1-18 were pending in this application when last examined.

Claims 1, 2, 7, 8, 10-12, 14-16 and 18 were examined on the merits and stand rejected.

Claims 3-6, 9, 13 and 17 were withdrawn as non-elected subject matter. Applicants reserve the right to file a Continuation or Divisional Application on any cancelled subject matter.

Claims 7, 8 and 10-12 were objected to.

Claims 1, 2, 7, 9-11, 14-16 and 18 are cancelled without prejudice or disclaimer thereto.

Claim 8 is reformulated into a method claim. The amino acid sequence of the polypeptide used in the method of claim 8 is limited to the specific sequence based on the description of page 14, lines 5 to 13, of the English specification. The method for cell internalization of a biologically active substance of claim 8 comprises a step of contacting the target cells with the substance and the polypeptide based on the description of page 19, lines 11 to 23.

Further, it is noted that claim 8 as filed was directed toward "use". Applicants note such inherently indicates a method. Thus, Applicants respectfully request the Examiner to examine this claim.

Claim 12 is amended according to the amendments of Claim 8.

Thus, no new matter has been added.

II. FOREIGN PRIORITY

In item 12(a) on page 1 of the Office Action, it is indicated that the certified priority documents have not been received. Attached herewith is a copy of PCT/IB/304 showing that the priority documents have been submitted. Applicants respectfully request acknowledgement of receipt of the priority documents.

III. SPECIFICATION/CLAIM OBJECTIONS

On page 2, the Office objected to the specification for the noted informality. The specification has been amended as suggested. Support for such amendment can be found in the same paragraph at line 5 in the specification. No new matter has been added by this amendment.

Further, on pages 2-3, claims 7, 8 and 10-12 were objected to for informalities. This objection is overcome, as applied to the remaining amended claim for reasons which are self-evident.

IV. INDEFINITENESS REJECTION

On pages 3-4 of the Office Action, claims 1, 2, 8, 14-16 and 18 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the noted reasons. Claim 8 is the only remaining claim. This rejection is overcome as applied to amended claim 8. In particular, this claim now recites active steps as suggested by the Examiner.

V. 101 REJECTION

On page 4 of the Office Action, claim 8 was rejected under 35 U.S.C. 101 for recitation of use without steps. Such claim has been amended to recite steps and therefore this rejection is moot.

VI. WRITTEN DESCRIPTION/ENABLEMENT REJECTIONS

On pages 5-9, claims 1, 2, 7, 8, 10-12, 14-16 and 18 were rejected under 35 U.S.C. § 112, first paragraph, for failing to meet the enablement requirement. Further, on pages 9-12, these claims were also rejected under 35 U.S.C. 112, first paragraph, for failing to meet the written description requirement.

It is noted that claim 8 and 12 are the only remaining claims subject to this requirement. It is further noted that claim 8 is amended as follows:

"A method for cell internalization of a biologically active substance comprising, a step of contacting target cells with a biologically active substance and a polypeptide, said polypeptide consisting of an amino acid sequence of SEQ 1D NO:2 having the amino acid

sequences of -Cys-Gly-Pro-Ser, -Cys-Pro-Tyr-Ser, -Cys-Pro-His-Ser or -Cys-Pro-Pro-Ser at positions 32 to 35 thereof."

(i) The results of Example 2 of the present invention clearly indicate that the modified thioredoxin consisting of an amino acid sequence of SEQ ID NO: 2 having the amino acid sequences of -Cys-Gly-Pro-Ser at the position of 32 to 35 exhibits an excellent cell internalization ability.

A person having ordinary skill in the art would easily predict that an amino acid sequence of SEQ ID NO: 2 having the amino acid sequences of -Cys-Gly-Pro-Ser, -Cys-Pro-Tyr-Ser, -Cys-Pro-His-Ser or -Cys-Pro-Pro-Ser at the positions of 32 to 35 also have the same ability. The reason is explained below.

(ii) Example 2 of the present invention discloses in Item 2 (i.e., under the title of 2. cell internalization on page 19) that Cys-Gly-Pro-Ser (modified TRX-C35S) exhibited an excellent cell internalization ability (see page 19, lines 11 to 23). The present specification also discloses (on page 13, line 19 to page 14, line 4) that "modified TRX having the substitution at position 35 with another amino acid such as Ser is bound to a cell surface at Cys of position 32, no binding to the cell surface occurs at position 35 because of no Cys at position 35 and consequently the modified TRX is rapidly internalized into the cell". In other words, the cell internalization of modified TRX occurs due to the lack of Cys32 -Cys35 binding, which is necessary for the redox activity in a wild-type TRX by the replacement of Cys at position 35 of TRX with another amino acid, and subsequently a thiol group of Cys at position 32 becoming free. This is also clear from the disclosure of Item 2 of Example 2 that the cell internalization was not observed in a wild-type TRX and modified TRX (TRX-C32SC35S) wherein Cys both at positions 32 and 35 were replaced with Ser. Therefore, it is predictable that the same result will be attained by removing or specifically masking the SH group of Cys at position 35 from the amino acids in the active center of TRX.

(iii) In the examples of the present invention, the cell internalization activity was confirmed in a modified TRX having the amino acid sequences of Cys-Gly-Pro-Cys. However, because not only the amino acid sequences of Cys-Gly-Pro-Cys but also the amino acid sequences of -Cys-Pro-Tyr-Cys-, -Cys-Pro-His-Cys- and -Cys-Pro-Pro-Cys- appear in the active center, it is

common general technical knowledge in this field that a modified TRX having those amino acid sequences has a similar level of TRX activity.

(iv) For example, as shown in "Drug News Perspect 15 (9), November 2002: pp. 575-580" **Attachment A**, -Cys-Pro-Pro-Cys- belongs to the thioredoxin superfamily (on page 578, TABLE 1: THIOREDOXIN SUPERFAMILY). This document also discloses that a polypeptide having such active site exhibits thioredoxin-like activity (page 577, right column, lines 4 to 15).

(v) "Eur. J. Biochem. 144, 417-423 (1984)", **Attachment B**, discloses that both glutaredoxin having the amino acid sequences of -Cys-Pro-Tyr-Cys- and thioredoxin (Cys-Gly-Pro-Cys) belong to the thioredoxin superfamily (page 421, left column, lines 16 to 18). As described above, it is known that all of the polypeptides that belong to the thioredoxin superfamily have activity similar to that of thioredoxin. Note that the fact that glutaredoxin has the amino acid sequences of -Cys-Pro-Tyr-Cys- is disclosed on page 417, left column, lines 20 to 24.

(vi) In terms of -Cys-Pro-His-Cys-, "Journal of Bacteriology, Feb. 2000, pp. 723-727", **Attachment C**, discloses that thioredoxin 1 having DsbA sequence (Cys-Pro-His-Cys) is highly compatible with thioredoxin (Cys-Gly-Pro-Cys) (on page 727, left column, lines 48 to 49). Note that the document discloses that the DsbA sequence is Cys-Pro-His-Cys on page 723, right column, lines 29 to 30.

(vii) Therefore, in any polypeptides other than -Cys-Gly-Pro-A-, when position A of -Cys-Pro-Tyr-A-, -Cys-Pro-His-A-, or -Cys-Pro-Pro-A- is replaced with Ser, the cell internalization should be improved accordingly.

Thus, the amended claim 8 meets the requirements under 35 U.S.C. 112, first paragraph. This rejection is therefore untenable.

VII. ANTICIPATION REJECTION

On pages 12-16, claims 1, 2, 7, 8, 10-12, 14-16 and 18 were rejected under 35 U.S.C. 102(b) as anticipated by Liu et al.

Applicants respectfully traverse this rejection as applied to the remaining amended claims.

Liu discloses the mutants of Trx-C23S, Trx-C35S and Trx-C32S/C35S double mutant. However, Liu merely describes that these mutants have an inhibition effect on apoptosis, and nowhere mention the use of these modified thioredoxin for cell internalization of a biologically

active substance.

Therefore, amended claim 8 has novelty over Liu.

It is clear from examples (especially item 2 of Example 2) of the present application, the modified thioredoxin of C35S has excellent cell internalization effects.

Even a person skilled in the art would not have been able to conceive of the present invention based on the disclosure of Liu, which is silent about the cell internalization effect of the specific modified TRX.

Therefore, amended claim 8 is unobvious over Liu.

Claim 12 is dependent on claim 8. Therefore, claim 12 is also novel and unobvious over Liu.

CONCLUSION

In view of the foregoing amendments and remarks, it is respectfully submitted that the present application is in condition for allowance and early notice to that effect is hereby requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

Respectfully submitted,

Yasuyuki ISHII et al.

/William R. Schmidt, II/

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